REMARKS/ARGUMENTS

The following remarks are responsive to the points raised by the Office Action dated August 6, 2008. In view of the following remarks, reconsideration is respectfully requested.

The Pending Claims

Claims 1-40 are pending, of which claims 23-40 are currently under examination, and claims 1-22 are withdrawn.

Rejections under 35 U.S.C. § 103

Claims 23-35, 37 and 38 were rejected under § 103 as unpatentable over Dudley et al., *J. Immunotherapy* 24: 363-373 (2001) (hereinafter, "Dudley 2001") or WO '97/05239 (hereinafter, "WO '239") in view of U.S. Patent No. 6,447,767 to Slavin et al. (hereinafter, "Slavin") and Riddell et al., *J. Immunol. Method* 128: 189-201 (1990) (hereinafter, "Riddell"), and U.S. Patent 5,126,132 to Rosenberg (hereinafter, "Rosenberg").

Claims 36, 39, and 40 were rejected under § 103 as unpatentable over Dudley 2001 or WO '239 in view of Slavin , Rosenberg, and Riddell, as applied to claims 23-35, 37 and 38 above, and further in view of Kawakami et al. *PNAS* 91: 6458-6462 (1991) (hereinafter, "Kawakami") and Stevens et al. *J. Immunol.*, 154: 762-771 (1995) (hereinafter, "Stevens").

Each of these rejections is separately and respectfully traversed.

Independent claim 23 is directed to a method of promoting the regression of a cancer in a mammal, comprising, *inter alia,* (i) administering to the mammal nonmyeloablative lymphodepleting chemotherapy, and (ii) subsequently administering autologous T-cells, which have been previously isolated and selected for highly avid recognition of an antigen of the cancer by stimulation of the T-cells *in vitro* with the antigen of the cancer, followed by one cycle of rapid expansion using irradiated allogeneic feeder cells, OKT3 antibody, and IL-2.

The presently claimed method is patentable because, contrary to the expectations of one of ordinary skill in the art at the time the instant application was filed, the presently claimed method provides unexpectedly superior objective clinical responses as compared to

methods in which patients were *not* administered nonmyeloablative lymphodepleting chemotherapy and in which the T-cells had undergone *multiple* cycles of rapid expansion. In support of the patentability of the instant claims, the Applicants submit herewith a Declaration under 37 C.F.R. § 1.132 by Dr. Mark E. Dudley.

At the time the instant application was filed, one of ordinary skill in the art would not have expected a method in which (i) administering to the mammal nonmyeloablative lymphodepleting chemotherapy, and (ii) subsequently administering autologous T-cells, which have been previously isolated and selected for highly avid recognition of an antigen of the cancer, followed by *one* cycle of rapid expansion, as claimed, would produce positive, objective clinical responses in patients. As Dr. Dudley explains, studies in which patients were *not* administered nonmyeloablative lymphodepleting chemotherapy and in which the T-cells had undergone *multiple* cycles of rapid expansion have produced poor objective clinical responses, as measured by the Response Evaluation Criteria in Solid Tumors (RECIST) or World Health Organization (WHO) criteria (the two currently acceptable clinical standards) (Dudley Dec., ¶ 4).

For example, Dr. Dudley explains that in Dudley 2001, 12 patients that had not been administered nonmyeloablative lymphodepleting chemotherapy were treated with 51 total infusions of cloned lymphocytes that underwent multiple cycles of rapid expansion (see, e.g., abstract, p. 365, right col. to p. 366, left col.; Dudley Dec., ¶ 5). As Dr. Dudley further explains, zero patients had detectable transferred cells in the blood at two weeks (see, e.g., p. 370, right col.; Dudley Dec., ¶ 5). In addition, no patient in this study demonstrated an objective response of a greater than 50% reduction in all lesions and no new lesions, and all patients were considered nonresponders (see, e.g., p. 371, left col. Dudley Dec., ¶ 5).

Accordingly, as Dr. Dudley further explains, one of ordinary skill in the art would recognize that this study resulted in *zero* objective responses as measured by the RECIST or WHO criteria (Dudley Dec., ¶ 6).

In another example, Dr. Dudley explains that in Yee et al., *PNAS,* 99: 16168-73 (published online Nov. 11, 2002) (hereinafter, "Yee;" copy attached), 10 patients that had not been administered nonmyeloablative lymphodepleting chemotherapy were treated with 43 total infusions of cloned lymphocytes that underwent multiple cycles of rapid expansion (see,

e.g., abstract; page 16168, right col.; Dudley Dec., ¶ 7). As Dr. Dudley further explains, zero patients had detectable transferred cells in the peripheral blood at three weeks (p. 16172, right col.; Dudley Dec., ¶ 7). In addition, the treatment resulted in disease stabilization in 5 out of 10 patients and a minor or mixed response in 3 out of 10 patients (see, e.g., page 16171, right col.; Dudley Dec., ¶ 7).

Accordingly, as Dr. Dudley further explains, one of ordinary skill in the art would recognize that the Yee study also resulted in *zero* objective responses as measured by the RECIST or WHO criteria (Dudley Dec., ¶ 8).

Therefore, based on the results obtained in Dudley 2001 and Yee, one of ordinary skill in the art at the time the instant application was filed would not expect that T-cells that had undergone only one cycle of rapid expansion, as claimed, would result in a positive, objective clinical response in patients, as explained by Dr. Dudley (Dudley Dec., ¶ 9).

However, contrary to the expectations of one of ordinary skill in the art at the time the instant application was filed, methods in which patients *were* administered nonmyeloablative lymphodepleting chemotherapy and, subsequently, were administered T-cells which had undergone *one* cycle of rapid expansion, as claimed, have produced positive, objective clinical results as measured by RECIST criteria, as Dr. Dudley explains (Dudley Dec., ¶ 10).

As Dr. Dudley explains, in Example 1 of the instant application, 13 patients received nonmyeloablative lymphodepeleting chemotherapy and, subsequently, were administered autologous T-cells which had been previously isolated and selected for highly avid recognition of an antigen of the cancer, the regression of which is to be promoted, by stimulation of the T-cells *in vitro* with the antigen of the cancer, followed by one cycle of rapid expansion using irradiated allogeneic feeder cells, OKT3 antibody, and IL-2 (Dudley Dec., ¶ 11). As attested to by Dr. Dudley, six of the 13 patients had objective clinical responses to treatment and four others demonstrated mixed responses with significant shrinkage of one or more metastatic deposits (Dudley Dec., ¶ 11). As further explained by Dr. Dudley, objective tumor regression was seen in the lung, liver, lymph nodes, and intraperitoneal masses, and at cutaneous and subcutaneous sites (Dudley Dec., ¶ 11). Moreover, five patients, all with evidence of concomitant cancer regression, demonstrated signs of autoimmune melanocyte destruction (Dudley Dec., ¶ 11). These results were

published in Dudley et al. *Science* 298: 850-854 (published online Sept. 19, 2002) (hereinafter, "Dudley *Science* 2002;" copy attached).

As Dr. Dudley further explains, the study described in Example 1 of the instant application was expanded as described in Dudley et al., *J. Clin. Oncol.*, published ahead of print on Sept. 22, 2008[1] (hereinafter, "Dudley 2008;" copy attached) (Dudley Dec., ¶ 12). As explained by Dr. Dudley, in Dudley 2008, 43[2] patients were administered nonmyeloablative lymphodepleting chemotherapy and, subsequently, received 46 total infusions of autologous T-cells, which have been previously isolated and selected for highly avid recognition of an antigen of the cancer, the regression of which is to be promoted, by stimulation of the T-cells *in vitro* with the antigen of the cancer, followed by one cycle of rapid expansion using irradiated allogeneic feeder cells, OKT3 antibody, and IL-2 (see, e.g., p. 2; Dudley Dec., ¶ 12).

In contrast to the results obtained in Dudley 2001 and Yee, the Dudley 2008 method resulted in objective, clinical responses measured by RECIST criteria in 21 out of the 43 patients (48%), as attested to by Dr. Dudley (see, e.g., Table 2; Dudley Dec., ¶ 12). Moreover, as Dr. Dudley further attests, tumor regression was seen in metastases at virtually all visceral and soft tissue sites including brain (Dudley Dec., ¶ 12). In addition, Dr. Dudley further attests that a majority of patients had detectable levels of transferred cells in circulation at one month after treatment (data not shown in Dudley 2008 paper; Dudley Dec., ¶ 12).

Accordingly, contrary to the expectations of one of ordinary skill in the art at the time the instant application was filed, a method in which patients *are* administered nonmyeloablative lymphodepleting chemotherapy and, subsequently, are administered T-cells which have undergone *one* cycle of rapid expansion, as claimed, have unexpectedly produced positive, objective clinical results, as shown, for example, in Dudley 2008 (Dudley Dec., ¶ 13). The positive, objective clinical results include tumor regression in virtually all visceral and soft tissue sites and superior persistence of the transferred cells in the blood.

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[1] Available at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2008.16.5449.

[2] The 43 patients in the study of Dudley 2008 includes the thirteen patients of Example 1 of the instant application which are referred to in the Dudley Declaration, ¶ 11.

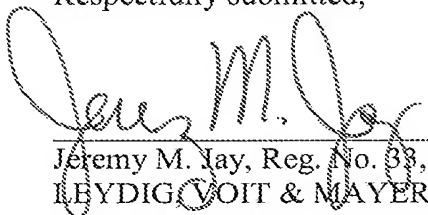
Because the claimed method produces unexpectedly superior objective clinical responses as compared to the methods of Dudley 2001 and WO '239, in which patients were *not* administered nonmyeloablative lymphodepleting chemotherapy and in which the T-cells had undergone *multiple* cycles of rapid expansion, the obviousness rejection cannot be maintained.

Since independent claim 23 is patentable for the reasons set forth above, the dependent claims are also allowable because they depend from allowable independent claim 23.

Conclusion

Applicants respectfully submit that the patent application is in condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,



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Amendment or ROA - Regular (JMJ/SML/mlg)